Opioid-Free Orthopaedic Surgery

CORE Study Group
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Title: Opioid-Free Orthopaedic Surgery

Research Question(s):

1. Can an opioid-free, multi-modal pain management pathway provide patients with a safe and predictable alternative to a conventional opioid-based pain management regimen?

2. Is there a difference in rates of complications, side-effects, and overall satisfaction between the two groups?

3. What are the barriers of enrollment and outcomes of patients that refuse study enrollment and do they differ from the study patient population?

Background and Significance:

Opioid-based analgesia has been a cornerstone of patient care in the setting of acute pain for the last century and has undergone logarithmic increase over the past twenty years. Unfortunately, the rise in utilization has brought with it a rise in opioid-induced side effects. These include constipation, nausea/vomiting, hyperalgesia [1, 2], delirium [3], addiction/withdrawal (with 67% of those prescribed a long-term opioid program still on opioids at an average of 4.8 years of follow-up [4]), and in some cases even respiratory depression/death. Patient expectations of opioid-based pain medication has driven a rapid rise in outpatient opioid prescriptions including both short and long-acting opioids [4]. These prescriptions have in turn become a source of significant mortality in the United States, with nearly 20,000 deaths due to opioid overdose in 2014 alone.

There have been momentous efforts made in identifying synergistic compounds to use for acute pain management in the perioperative time period to begin to minimize the opioid requirement for pain control. These studies have focused on nerve modulation with gabapentinoids [5-7], intravenous and local administration of sodium-channel blockers such as lidocaine and bupivacaine [8-10], and increased interest in non-steroidal anti-inflammatories and acetaminophen [11-15]. At this time, no study has looked at the possibility of utilizing a multi-modal acute post-surgical pain control pathway that did not include some form of opioid medication for the general population.

Total Shoulder Arthroplasty (TSA), Reverse Total Shoulder Arthroplasty (RTSA), Total Hip Arthroplasty (THA), Carpometacarpal (CMC) Arthroplasty, Knee Arthroscopy, Anterior Cervical Discectomy and Fusion (ACDF), Anterior Cervical Disc Arthroplasty (ACDA), Hallux Valgus, and Hallux Rigidus procedures continue to be dominant procedures in the orthopaedic armamentarium and account for well over a million surgeries done in the United States per year. With the ability to utilize targeted nerve blocks by anesthesia [16-18], and the increasing data showing efficacy of multi-modal therapy for acute pain [19-24], we propose a patient care pathway that is completely free of all opioid-based medications. From the time that patients are checked in until the time the patient follows up in clinic, they will utilize a pathway designed to eliminate pain and opioid-related side effects following the previously mentioned procedures. Our hope is that well-designed pathways for these surgeries can quickly be modeled for other surgical procedures in an attempt to minimize the negative effects of opioid utilization both acutely and on a societal level.

Purpose of Study:
To compare the safety and effectiveness of two pain control pathways following routine orthopaedic surgical procedures (single level or two-level ACDF/ACDA, 1st CMC arthroplasty, Hallux Valgus/Rigidus corrections, diagnostic knee arthroscopies, total hip arthroplasty, and total shoulder arthroplasty / reverse total shoulder arthroplasty). The control group will undergo surgery with an opioid-based pain protocol and the intervention group will undergo surgery with a multimodal, opioid-free protocol.
Patients will have data collected with respect to pain scores, overall comfort level, overall satisfaction with the surgical experience and recovery, constipation, falls, and overall satisfaction with pain control, in addition to procedure-specific outcome scores and patient-specific metrics.

Study Design:

Type of Study
Randomized Clinical Trial ; with a nested, Observational arm of the same Clinical Trial.

Treatment Group:
The treatment group will consist of patients who undergo surgery and treatment without the use of opioids. Medication administration is based on the surgery being performed (see **Appendix 1** for full list of medications per surgery):

- Pre-operative Management
  - In the preoperative area, every patient will receive an oral (PO) dose of both gabapentin [30] and meloxicam along with intravenous (IV) doses of Tylenol and Zofran. If IV Tylenol is not available at the surgery location, PO Tylenol may be used as a substitute.
  - Patients under the age of 75 will be given a Scopolamine Patch.

- Intra-operative Management
  - General Anesthesia:
    - If indicated based on procedure type, general anesthesia will be performed with a completely opioid-free regimen to include Propofol, ketamine, IV lidocaine, rocuronium/vecuronium, typical anesthetic gases including sevoflurane/desflurane. If the attending anesthesiologist deems it necessary to dose with opioids during the procedure, this will be recorded and reported.
    - Patients undergoing Total Hip Arthroplasty, Total Shoulder Arthroplasty, or Reverse Total Shoulder Arthroplasty may also be given Suggamadex to allow immediate paralysis reversal, allowing patients to have more accurate pain assessments in the recovery room.

  - Regional Anesthesia:
    - Procedures requiring Spinal anesthesia will receive 1.5-2.0cc 0.75% Bupivacaine as a single-shot, upright in the operating room.

- Procedures requiring Interscalene Blocks will be done under ultrasound guidance by a board certified anesthesiologist

- Procedures requiring Ankle Blocks may be done under ultrasound guidance by a board certified anesthesiologist at the anesthesiologist's discretion.

- Procedures requiring Hand Blocks will receive a low brachial plexus block. These blocks will be performed supraclavicular, infraclavicular, or axillary and may be done with mild versed sedation (no narcotic).

- Local Anesthesia:
  - A CERT (Clonidine, Epinephrine, Ropivacaine, Ketorolac) injection cocktail will be used during THA [28]
  - Liposomal bupivacaine or a CERT (Clonidine, Epinephrine, Ropivacaine, Ketorolac) injection cocktail will be used for all Shoulder arthroplasty procedures [29].
  - Local anesthetic to be utilized in other procedures (see **Appendix 1**)

- Adjunct Intra-operative medications
  - Other medications including Toradol, decadron, epinephrine, and/or clonidine may be utilized in select procedures (**Appendix 1**)

- Post-operative Hospital Care
  - After surgery, patients' pain will be managed with non-opioid modalities. This may include modalities such as IV Toradol, PO Tylenol, IV Tylenol, Gabapentin [31-33], Decadron, Meloxicam, and Cryotherapy.
  - There will be no study defined opioid rescue medication. For breakthrough pain the day of surgery (in-patient), all of the non-opioid pain modalities should be exhausted. If the patient continues to request pain medication, then the hospital staff will be instructed to consult with the study physician before prescribing a narcotic.

- Discharge Medications
  - Patients will be discharged with non-opioid medications to help manage pain after discharge from the hospital or surgery center. This may include modalities such as Toradol, Meloxicam, Gabapentin, Tylenol, Aspirin, and Cryotherapy.

  - Durable medical equipment will be provided to both groups (ie: sling, soft cervical collar).
  - When opioid-free patients leave the hospital (or surgery center), they will be provided instructions to call a designated study hotline if, outside of normal clinic hours, they are experiencing unacceptable amounts of uncontrolled pain. This hotline will notify the on-call provider that the patient is part of the opioid-free research study. At this point, the on-call provider will work with the patient to

identify the problem, evaluate the severity of the patient's pain, identify what medications (and how much) have been taken, confirm that the patient has taken all medication as prescribed and is using cryotherapy appropriately. If these steps do not satisfactorily resolve the patient's pain, opioid-free treatment options have been exhausted, the patient continues to have unacceptable, uncontrolled pain, and the patient requests alternative medications from the opioid-free pathways, then the on-call provider may prescribe alternative medication or send the patient to an urgent care or emergency room to treat pain.

Control Group:
The control group will not differ from the surgeon's routine management pathway. Anesthesia should be utilized in a routine fashion with all routine perioperative medications. Patients will be discharged on routine postoperative medications including opioids, NSAIDS, and any other modalities typically used by the treating surgeon. Medication administration is based on the surgery being performed (see **Appendix 2** for full list of medications per surgery). The control group for Total Hip Arthroplasty will slightly vary in that recent literature shows the effectiveness of a multimodal approach in managing perioperative pain [28]. All data and data collection methods will mirror the intervention arm.

*If an unforeseen drug shortage arises, the morphine milliequivalents of an alternative pain medicine will be prescribed. i.e. Hydromorphone IV replaced with Morphine (1.2 mg for pain 4-6, 2 mg for pain 7-10)

Observational Arm:
Patients who are not willing to be randomized to their postoperative pain management will be asked to participate in the observational arm of the study. The same data points will be collected on these patients, but the patient and their surgeon will be able to decide which pain management pathway they receive (opioid-free, or control protocol)

Eligibility Criteria

Inclusion Criteria

1. Patient is scheduled to undergo one of the following procedures:
    - Primary single-level or two-level ACDF or ACDA for degenerative disease
    - Primary 1st CMC arthroplasty
    - Primary Hallux Valgus or Hallux Rigidus correction
    - Diagnostic knee arthroscopy +/- meniscal debridement
    - Elective primary total shoulder or reverse total shoulder arthroplasty
    - Primary total hip arthroplasty

Exclusion Criteria

1. Revision surgery for one of the study-specific procedures
2. Chronic opioid therapy – per investigator discretion
3. Significant liver disease – (NOTE: Patients with a history of liver disease will have a hepatic panel drawn to be reviewed by the study investigator to assess if the values are within acceptable limits for inclusion in the study)
4. Fracture or soft tissue injury
5. Sickle cell disease
6. Workers compensation
7. Alcohol dependence
8. Contra-indication to regional anesthesia
9. History of gastrointestinal (GI) bleeding or peptic ulcer
10. History of bleeding problems
11. Patients taking anticoagulants, not including aspirin (only applies to Randomized portion of study. These patients can still participate in Observational Control Group)
12. Renal insufficiency – Creatinine clearance less than 30 mL/min (only applies to patients having surgery requiring NSAIDs treatment)
13. Hammertoe in isolation (Hallux Valgus/Rigidus exclusion only)
14. Concomitant meniscal repair or microfracture (Knee Arthroscopy exclusion only)
15. Ineligible for spinal anesthesia (THA exclusion only)
16. Previous ipsilateral hip surgery, not including hip scope (THA exclusion only)
17. Allergy to non-steroidal anti-inflammatory medications (NSAIDs)

Definition of Variables

Primary Outcome Variable:
Pain at patient discharge or 24-hours postoperatively, whichever comes first – measured on a 0-10 numeric rating scale (NRS).

Secondary Outcomes Variables:

a. Pain at 6hr, 12hr, 2 weeks, 6 weeks, and 1 year post-operatively measured on a 0-10 NRS
b. Nausea (Y/N)
c. Constipation (Y/N)
d. Continued use of pain medications (Y/N)
e. Satisfaction with overall pain control
f. Satisfaction with overall surgical experience
g. VR-12 (quality of life)
h. RS-5 (resilience)
i. PAC-SYM (constipation)
j. At home falls (value)
k. Post-Operative opioid use
l. Length of hospital stay (Date of Discharge-Date of Surgery (hrs))
m. Surgical Site Infection (SSI)
n. Deep infection
o. Dehiscence

p. GI Bleed or Peptic Ulcer Disease (diagnosed within 1 year)
q. Acute renal failure
r. Readmission (within 1 month)
s. Reoperation (related to surgery)
t. For Control Group: What has been done with unused opioid pills?
u. For Control Group: If opioid pills are disposed, how were they disposed?
v. For Control Group: If opioid pills are not disposed, how are they secured?

Secondary Outcomes Variables collected in-hospital, as applicable:

w. Delirium (Y/N)
x. Falls (Y/N)
y. Morphine milli-equivalents (In-hospital operative, In-hospital post-operative, and post-discharge) (value)
z. Intraoperative Complications
aa. Overall comfort level, measured on a 0-10 NRS (taking into account pain, nausea, mentation, and overall well-being)
bb. Length of surgery (incision to dressing on)

Secondary Outcomes Variables (Function):

(- indicates as appropriate per surgery performed)*

cc. Central Sensitization Inventory Questionnaire
dd. *American Shoulder and Elbow Surgeons (ASES) Shoulder Score *(*TSA/RTSA patients)*
ee. *Simple Shoulder Test *(*TSA/RTSA patients)*
ff. *Patient Rated Wrist Evaluation (PRWE) *(*CMC Arthroplasty patients)*
gg. *Disabilities of the Arm Shoulder Hand (DASH) *(*CMC Arthroplasty patients)*
hh. *Foot and Ankle Ability Measure (FAAM) *(*Hallux Valgus/Rigidus patients)*
ii. *Neck Disability Index (NDI) *(*ACDF/ACDA patients)*
jj. *D*ysphagia Short Questionnaire *(*ACDF/ACDA patients)*
kk. *HOOS Jr. *(*THA patients)*
ll. *KOOS *(*Knee Arthroscopy patients)*

Secondary Outcome Variables (Radiographic)

mm. Neer score *(*TSA/RTSA patients*
nn. Bony bridging anteriorly and/or through disc space (**ACDF)*
oo. O-SS Score (**THA*)
pp. Callus formation on AP and lateral radiographs and absence of radiolucent lines (**Hallux Valgus/Rigidus*)

<u>Independent Variables/Covariates/Confounding Variables</u>

a. Age
b. Gender
c. Height/Weight/Body Mass Index (BMI)
d. Tobacco Use (current, former, never)
e. Medical Comorbidities (based on the Charlson Comorbidity Index)
f. Primary Diagnosis
g. Pre-Operative Opioid Use (Y/N)

h. Pre-Operative current and average pain score (NRS) (value)
i. Pre-Operative creatinine level
j. Surgeon
k. Surgical Approach
l. Concomitant Procedures
m. Date of Surgery
n. Alcohol or other non-prescribed medication self-use to help with comfort
o. Tourniquet time
p. Additional surgery information

Methodology

Patient Selection and Identification:
Patients will be initially identified after workup and evaluation by staff physician and are diagnosed and determined to require one of the following procedures:

- Primary Hallux Valgus or Hallux Rigidus correction
- Primary 1st CMC arthroplasty,
- Primary single-level or two-level ACDF or ACDA for degenerative disease,
- Primary Total Hip Arthroplasty,
- Primary or Reverse Total Shoulder Arthroplasty, or
- Diagnostic knee arthroscopy +/- meniscal debridement.

Patient recruitment:
The surgeon will introduce the concept of opioid-free vs. opioid-based pain management after surgery. All inclusion/exclusion criteria and patient demographics will be reviewed. After identification, interaction will be conducted with the patient, physician, and research staff to offer participation in the randomized study and obtain written consent and authorization for participation.

If the patient agrees to be randomized, written consent and authorization for participation will be obtained.

If patients decline participation in the randomized study, the option of collecting data as part of an observational study will be presented to the patient. All data collection and procedures for the control and opioid-free treatments in the observational study will be identical to the randomized study, with the exception of the randomization itself. Written consent and authorization for participation will be obtained from the observational group of patients.

The study consent will be scanned in the clinic and hospital chart to identify the patient as a study patient.

Screening Visit:

After written consent is obtained, the screening visit will include a series of questionnaires (dependent upon the type of surgery being performed) and physical exam. The questionnaires will

ask questions about their level of pain, function, presence of constipation, and satisfaction with their pain control. The exam will include an assessment of range of motion, when applicable. All patients will be asked to complete a Resilience Questionnaire at the screening visit only.

All patients (with the exception of non-THA Observational Study patients) will have a blood draw (approximately 5 milliliters, or about 1 teaspoon) to determine eligibility based on creatinine clearance. One tube of blood will be collected in a gold serum top vacutainer tube (approximately teaspoons) by the research staff in the clinic during the screening visit. It will be sent to the local lab for processing. Creatinine clearance will be calculated with the Cockcroft-Gault Formula:

$$CC = [(140 - age_{years}) * weight_{kg}]/(72 * Creatinine_{Serum}\left(\frac{mg}{dl}\right))$$

For females, the calculated value is multiplied by 0.85 (i.e., 85% of the calculated value). For males, there is no additional conversion necessary. For convenience, an online creatinine clearance calculator will be used (http://www.mcw.edu/calculators/creatinine.htm) for the calculation. The resulting creatinine clearance will be recorded. Patients with a creatinine clearance of less than 30 mL/min will be excluded from the study all together. Patients with creatinine clearance between 30 and 60 mL/min will receive a half-dose of all NSAIDs if enrolled in the intervention arm of the study. Patients with creatinine clearance greater than 60 mL/min will be eligible to receive full doses of NSAIDs in the intervention arm of the study.

Patients who identify as having liver disease will also receive another blood draw (approximately 5 milliliters, or about 1 teaspoon) to evaluate hepatic liver enzymes.

Randomization:

Patients who consented to participate in the randomized study will be randomized in a 1:1 fashion to one of the two treatment groups. Patients will be randomized to either receive Control Treatment or to receive Intervention (opioid-free) Treatment. Randomization will occur within one week of their surgery. A random number generator will be used to determine the randomization schedule and allocation will be assigned using REDCap. The allocation will be communicated to the surgical team via a randomization email and a randomization form will be placed on the patient chart, prior to surgery.

Randomization will not occur for patients who consented to participate in the observational study. Observational study patients will have the choice to follow the control or opioid-free pathways.

Procedure Data Collection

The patient will be identified as a research patient on the hospital chart. Their randomization will be listed.

Opioid-free group:

Communication with the anesthesia team will take place the day before surgery to identify the patient as an opioid-free participant, and a reminder will be provided while the patient meets with the anesthesiologist in pre-op.

All patients will have their medication recorded during their hospitalization. For in-patient procedures, a Delirium Score, Comfort Level, and Pain Score will be recorded at 6hr, 12hr, and 24hr (or discharge). These evaluations will also be done for any out-patient procedures who are still in the hospital at the 6hr 12hr, or 24hr time points.

All patients will leave the hospital (or surgery center) with a diary to record their pain, comfort, and medication usage. Patients undergoing ACDF/ACDA surgery will also receive a diary to record their compliance with using the Soft Collar equipment.

Patients who leave the hospital (or surgery center) prior to the 24hr pain score being collected will be contacted by study staff 24 hours after surgery to collect a Pain Score.

Follow-up Visits:

All patients will be followed up at the following intervals:

- 2 weeks postop
- 6 weeks postop
- 1 year postop

Schedule of events table:

Procedure	**Preop/Screen**	**Op**	**6 hour**	**12 hour**	**24 hour**	**2 week**	**6 week**	**1 year**
ICF	X							
Demographic	X							
Comorbidities	X							
Resilience Questionnaire (RS-5)	X							
Central Sensitization Inventory	X							
Creatinine Clearance	X							
Randomization	X *(within one week prior to surgery)*							
Complications (nausea, constipation, falls)			X***	X***	X***	X	X	X
Delirium Score (CAM25)***			X***	X***	X***			
Patient Comfort Level (NRS)***			X***	X***	X***			
ConMeds (specifically anti-emetic/nausea and pain medication)	X	X	X***	X***	X***	X	X	X
Surgical & Hospital-Stay Information		X						
Pain Score (NRS), current	X		X	X	X	X	X	X
Pain Score (NRS), average	X					X	X	X
Constipation Questionnaire (PAC-SYM)	X					X	X	X

Patient Reported Outcomes Questionnaires *(specific to applicable surgery)*	X					X	X	X
Patient Pain (NRS) Diary±						X		
Patient Comfort (NRS) Diary±						X		
Patient Pain Medication Diary±						X		
Patient Collar Compliance Diary± *(ACDF/ACDA patients only)*						X		

*** Only applies to inpatient procedures
± The diaries will be completed daily from day of discharge until the 2 week visit. They will be collected at the 2 week visit.

Quality Improvement Survey:
Subjects whose study participation placed them in the Opioid-Free Group will receive an optional survey to provide open-ended feedback to OrthoCarolina Research Institute on their experience undergoing treatment without the use of opioids. This survey will not undergo data analysis, but will serve as quality improvement and patient testimonials. The survey will contain questions such as, but not limited to:

- What were your initial concerns when you were introduced to the non-opioid pain pathway for your surgery?
    - Ultimately, did you find these concerns to be an issue by the end of your treatment?
- Do you feel like there were benefits to completing a non-opioid pain regimen? If yes, please describe.
- Would you recommend this opioid-free treatment route to your friends? Why or why not?
- Do you have a personal reason or story as to why you chose to participate in an opioid-free research study?
- Please share what your overall experience was like participating in the CORE research study.
- Is there any additional information or feedback that you would like to share?

Estimation of Sample Size:
The sample size estimate was calculated using data from a previous study comparing the pain NRS at 24 hours between the two groups. This is a noninferiority design with a 2 point margin. The mean pain score for the traditional group was 3.2 and the mean pain score for the opioid-free group was 2.5 with a pooled SD of 2.5. An alpha level of 0.5 and a minimum power of 80% yielded 50 patients per group per procedure. Therefore, the target sample size for the study is 300 completed patients at 24 hours in the traditional group and 300 completed patients at 24 hours in the opioid-free group.

Statistical Procedures:
Standard descriptive statistics will be reported including measures of central tendency, variance as well as frequencies and proportions. For bivariate analyses, chi-square or Fishers Exact tests will be used for categorical data to determine statistical differences. For normally distributed interval

or continuous variables a student T-test will be used. For non-normally distributed data a Wilcoxon rank sum test will be used. Multivariate analyses will be conducted as appropriate.

Data Management:

Data should be entered on at least a weekly basis, via REDCap (http://project-redcap.org/). REDCap is a secure web application designed exclusively to support data capture for research studies. It allows users to build and manage online surveys and databases quickly and securely with site and personnel specific usernames and passwords. REDCap provides audit trails for tracking data manipulation and user activity, as well as automated export procedures for seamless data downloads to Excel, PDF, and common statistical packages like SPSS, SAS, and Stata.

Data Safety Monitoring Plan

Serious adverse events (SAEs) that are "related," "probably related" or have an "unknown" relatedness to the study procedure, will be reported to the data safety monitoring board via email as they occur. The data safety monitoring board meets every other month. At each meeting the study will be reviewed for adverse events, serious adverse events, and overall feasibility issues.

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